REFERENCES

Galant SP, Haydik IB: Allergenicity of cow's milk formula hydrolysates. Pediatr Asthma Allergy Immunol 1991; 5:237-244

Kleinman RE: Cow milk allergy in infancy and hypoallergenic formulas. J Pediatr 1992; 121:S116-S121

Sampson HA, Bernhisel-Broadbent J, Yang E, Scanlon SM: Safety of casein hydrolysate formula in children with cow milk allergy. J Pediatr 1991; 118:520-525

Zeiger RS: Prevention of food allergy in infancy. Ann Allergy 1990; 65:430-442

Exercise-Induced Asthma and Anaphylaxis

ALTHOUGH EXERCISE is a salutary activity for many people, for others it may provoke anaphylaxis or asthma. Exercise-induced asthma and exercise-induced anaphylaxis rarely occur in the same person and are thus considered separate disorders. The common factor is the form of exercise, which is almost invariably intense running for relatively short periods.

Exercise-induced asthma is defined as a transitory increase in airway resistance that follows vigorous exercise. It can be reproduced in the laboratory in about 80% of patients with asthma who exercise at 80% to 90% of their predicted maximal working capacity for six to eight minutes while breathing room air. The severity cannot be predicted by the resting level of lung function. Even persons with normal lung function can suffer severe asthma within minutes of completing exercise. Inhalation of a β-adrenergic aerosol or cromolyn sodium before exercise will prevent the occurrence in 90% of people with this reaction. The rest require either larger than usual doses or a combination of drugs for relief.

Proposed mechanisms for airway narrowing include the release of mast cell mediators such as histamine, the stimulation of vagal afferent pathways, and reactive local hyperemia and edema initiated not by an immunologic response but by abnormal water loss in the airways. Water loss results from a combination of temperature drop in the bronchial mucosa and hyperosmolarity of the periciliary fluid. Exercise-induced asthma has been prevented by having a patient inhale warmed or moist air during exercise.

Exercise-induced anaphylaxis can develop in persons without a history of asthma or even any allergic condition, although about half appear to be atopic. The prevalence is unknown, but one center has seen 500 cases over a 17-year period. Patients typically have a sensation of cutaneous warmth and pruritus initially, followed rapidly by generalized erythema, urticaria, hypotension, and upper respiratory tract obstruction during physical activity. Asthma rarely occurs. Although the reactions appear life-threatening and may require medical therapy for anaphylaxis, deaths have not been reported. Most patients are adolescents or younger adults, but the condition has been reported in a 4-year-old child.

Exercise-induced anaphylaxis may require another factor, food ingestion, with the physical activity. Anaphylaxis develops in some patients only in association with either a meal followed by exercise or eating a specific food for which they have immunoglobulin E antibodies. Strangely enough, either factor alone in this group with food-dependent, exercise-induced anaphylaxis will not provoke a generalized reaction. In addition, a familial tendency has been found in some cases.

A common mechanism has not been found for these diverse forms of exercise-induced anaphylaxis. A release of mediators such as histamine has occurred in only about half of the patients studied. Some with food dependency may have exaggerated blood volume shifts from the skeletal muscle circulation to the splanchnic vasculature during food digestion; others have demonstrable autonomic nervous system dysfunctions. Shared leukocyte antigen haplotypes have been found in the familial form.

Treatment may be defined as active or preventive. Active treatment is identical to the treatment of any type of anaphylaxis. Prevention involves restriction or changing the form of exercise and, in the food-dependent type, permitting exercise only befu̇re food intake. Pretreatment with histamine-1 antagonists or gradual increments of exercise has not proved uniformly effective. Exercise-induced asthma and anaphylaxis can be readily diagnosed and ameliorated by preventive meaures.

HAROLD S. NOVEY, MD
Orange, California

REFERENCES

Broide HD, Eisman S, Ramsdell JW, Ferguson P, Schwartz LB, Wasserman SI: Airway levels of mast cell-derived mediators in exercise-induced asthma. Am Rev Respir Dis 1990; 141:563-568

Dohi M, Suko M, Sugiyama H, et al: Food-dependent, exercise-induced anaphylaxis: A study on 11 Japanese cases. J Allergy Clin Immunol 1991; 87:34-40

Silvers WS: Exercise-induced allergies: The role of histamine release. Ann Allergy 1992; 68:58-63

Antihistamines and the Heart

THE TOXICITIES OF classic, first-generation histamine-1–receptor antagonist antihistamines have produced sedation, decreased mental alertness, and anticholinergic side effects. Beyond scattered reports of palpitations or hypotension in antihistamine overdosage, few serious adverse cardiovascular reactions have been described with the use of these agents.

With the development of second-generation, nonsedating H_1-receptor blockers, the spectrum of side effects has changed. Terfenadine, a relatively short-acting antihistamine that is extensively metabolized by the hepatic cytochrome P-450 system, induces a small increase in the corrected QT interval on electrocardiography, even at recommended dosages. This electrocardiographic change is rarely clinically important. When terfenadine is administered to patients with impaired hepatic function or given simultaneously with the macrolide antibiotics erythromycin or troleandomycin or with the imidazole antifungals ketoconazole or itraconazole, the QT interval may be more dramatically prolonged. This has resulted in serious ventricular tachyarrhythmias (including torsades de pointes and ventricular fibrillation) and death. These agents appear to alter terfenadine pharmacokinetics and may cause the accumulation of terfenadine in certain patients.

Clarithromycin and azithromycin, newer macrolide antibiotics with minimal effects on hepatic cytochrome P-450, have not been evaluated for their interactions with terfenadine. The possible drug interactions between fluconazole and terfenadine have not yet been characterized. The concomitant administration of these agents with terfenadine is not recommended until more data are available. Other clinical conditions that alone may prolong the QT interval and possibly increase the likelihood of terfenadine cardiotoxicity include hypokalemia, hypomagnesemia, hypocalcemia, and the congenital QT syndrome.

Astemizole, a longer-acting nonsedating antihistamine, has been reported to cause a wide spectrum of cardiac dysrhythmias in patients with acute overdose but rarely at recommended dosages. In addition to torsades de pointes and other ventricular tachyarrhythmias with prolonged QTc interval, first- and second-degree atrioventricular blocks and bundle branch blocks have been described, the last particularly in children. Because of the long half-life of astemizole metabolites, several days of cardiac monitoring and supportive therapy are recommended in patients with overdose with this agent.

Because of more limited experience with two other second-generation antihistamines soon to be available in the United States, cetirizine and loratidine, the spectrum of cardiac toxicity with these agents is less clear. Cetirizine is excreted largely unchanged in the urine, and patients with impaired renal function could have prolonged half-lifes for this drug. Loratidine, like astemizole and terfenadine, is metabolized by the liver. In any case, careful consideration to possible drug interactions and long-term clinical conditions should be given before prescribing second-generation antihistamines.

DIANA MARQUARDT, MD
San Diego, California

REFERENCES

Honig PK, Woosley RL, Zamani K, Conner DP, Catilena LR Jr: Changes in the pharmacokinetics and electrocardiographic pharmacodynamics of terfenadine with concomitant administration of erythromycin. Clin Pharmacol Ther 1992; 52:231-238

Simons FE, Simons KJ: Second-generation H₁-receptor antagonists. Ann Allergy 1991; 66:5-21

Tobin JR, Doyle TP, Ackerman AD, Brenner JI: Astemizole-induced cardiac conduction disturbances in a child. JAMA 1991; 266:2737-2740

Vocal Cord Dysfunction Presenting as Asthma

WHEEZING OCCURS IN various organic lung diseases as a result of reversible or irreversible airway narrowing, localized endobronchial disease (such as tumor or sarcoidosis), and diffuse or localized lung disease (such as pulmonary edema, lymphangitic disease, or pulmonary embolism). Vocal cord dysfunction, a recently described syndrome that presents as asthma, is an uncommon but important asthma impersonator that should be included in every physician's differential diagnosis of asthma.

The pathophysiologic mechanism involved in vocal cord dysfunction is a dysfunction of the larynx in which the vocal cords are inappropriately adducted during inspiration, expiration, or both. The sound produced can be similar to asthmatic wheezing, and patients may be mistakenly diagnosed and treated for asthma. Missing this diagnosis has serious consequences, for many patients have received tracheotomies or been aggressively treated for asthma with systemic corticosteroids, producing iatrogenic Cushing's syndrome.

The clinical presentation is often dramatic, with a frightened patient reporting to an emergency department or physician's office with one of many attacks of profound wheezing and dyspnea. Patients are typically young women between the ages of 20 and 40. The syndrome has recently been reported in children as well. On examination, there are inspiratory and expiratory wheezes loudest over the larynx and less well transmitted to the chest wall. Arterial blood gas values are usually normal, as opposed to the hypoxemia seen in acute asthma, and pulmonary function studies show pronounced variability in spirometric test results. Laryngoscopy during wheezing shows almost complete adduction of the vocal cords, with the glottis reduced to a small posterior diamond-shaped opening. This finding and the wheezing it produces can be reversed by asking the patient to cough or breathe in a panting manner. If seen when an attack is not occurring, the patient will often report that the wheezing comes from the throat and not the chest.

Because true asthma and vocal cord dysfunction can coexist, the use of a methacholine challenge test to evaluate a patient's bronchial hyperresponsiveness should be done in most patients. A flow-volume loop characteristic of extrathoracic airways obstruction can be helpful.

The cause of the condition is not clear, but a hypothesis is that "suggestion" mediated by the vagus nerve may alter the laryngeal tone and lower the threshold for stimuli to produce vocal cord spasm. Recently there have been several reports of cases of vocal cord dysfunction associated with gastroesophageal reflux, which reversed with treatment of the reflux.

Vocal cord dysfunction presenting as asthma can have a psychological basis. The operative mechanisms that come into play include conversion reactions associated with a variety of conditions, such as depression, a passive-dependent personality, and somatization disorder. These patients do not knowingly control their illness for secondary gain, and therefore it is not considered malingering. Therapy consists of a multidisciplinary approach including the physician, psychiatrist, and speech therapist. The physician's role is to inform the patient of the findings, especially the absence of diseases such as asthma, and to explain the nature of the condition. Patients often express a positive reaction to the initial explanation, and such a reaction often implies a good prognosis.

It must be recalled that vocal cord dysfunction and true asthma may coexist; therefore, in an acute attack, the patient should be treated for asthma unless there is absolute proof that asthma is not the cause of the symptoms.

WILLIAM SOKOL, MD
Newport Beach, California